Lymphoscintigraphy and Radioguided Biopsy of the Sentinel Axillary Node in Breast Cancer

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Lymphoscintigraphy associated with radioguided biopsy of the sentinel node (SN) is well established in clinical practice for melanoma. In breast cancer, the SN concept is similarly valid, and lymphoscintigraphy is a useful method for localizing the axillary SN. The aim of this study was to optimize the lymphoscintigraphy technique in association with a gamma ray detecting probe (GDP) for identifying and removing the SN in breast cancer patients. **Methods:** Two-hundred fifty patients with operable breast tumor underwent lymphoscintigraphy before surgery. Three different size ranges of ^{99m}Tc-labeled colloid particles (<50, <80 and 200–1000 nm) were used, with either subdermal (above tumor) or peritumoral injection. Early and late scintigraphic images were obtained in anterior and oblique projections, and the skin projection of the detected SN was marked. Sentinel nodes were identified and removed with the aid of the GDP during breast surgery; they were tagged separately. Complete axillary dissection followed. In 40 patients, a blue dye was also administered in addition to subdermal radiolabeled colloid to compare blue dye mapping with lymphoscintigraphy localization. **Results:** Lymphoscintigraphy successfully revealed lymphatic drainage in 245 of 250 patients (98%). The axillary SN was identified in 240 patients (96%). SN biopsy correctly predicted axillary node status in 234 of 240 patients (97.5%). Lymphoscintigraphy and GDP detected the SN most easily and consistently when 200–1000 nm colloid was administered subdermally in an injection volume of 0.4 ml. Blue dye mapping was successful in 30 of 40 patients (75%). In 26 of these patients, the dye and lymphoscintigraphy identified the same node; in 4 cases different nodes were identified. None of these four patients had axillary disease. **Conclusion:** Lymphoscintigraphy is a simple procedure that is well tolerated by patients. Sentinel node identification is more reliable when large-size radiolabeled colloids are injected in a relatively small injection volume (0.4 ml). Use of a GDP greatly facilitates precise pinpointing and rapid removal of the SN.

Key Words: lymphoscintigraphy; sentinel node; gamma ray detecting probe; breast cancer

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A major aim of modern cancer surgery is to use less aggressive approaches while maintaining oncologic radicality (*1–3*). The development of imaging techniques and more sophisticated screening examinations has made it possible to identify malignant lesions at earlier stages so that new cancers are more often smaller in size and often may be treated less aggressively. This is especially true in breast cancer, in which clinically occult lesions are diagnosed with increasing frequency, and it is expected that, in a few years >50% of newly diagnosed breast cancers will be small (*4*).

For such cancers, the likelihood of axillary involvement is much reduced. Nevertheless, it is mandatory to stage the axilla because the information it provides is important for planning the most appropriate treatment. However, if it were possible to reliably determine whether or not the axilla is involved without

complete axillary dissection, this would enable a less aggressive surgical approach to the disease breast cancer because patients with a disease-free axilla could often be spared axillary dissection. The technique of sentinel node (SN) biopsy was conceived for this purpose.

First developed by Morton et al. (*5,6*) to select melanoma cases for regional node dissection, SN biopsy has been extended to other malignancies (*7–9*). In the field of breast cancer, initial studies were conducted in which blue dye was injected peritumorally and the first axillary node to take up dye was identified. These studies showed that the SN concept is biologically valid in breast cancer (*10*). However, the SN was missed in up to 40% of early cases as the surgical procedure of after the dye path from the tumor bed to the SN in the axilla is time-consuming and sometimes difficult; considerable experience was required to improve the success rate (*11*).

If a radioactive tracer is injected, then the SN can be identified by lymphoscintigraphy, and a gamma ray detecting probe (GDP) can be used to locate the skin projection of SN and assist biopsy. These techniques are already used successfully in melanoma and breast cancer (*12–15*). However, in breast cancer, the technique has yet to be optimized, and in particular, the ideal radioactive particle size, injection site and injection volume remain to be established.

In a preliminary report (*16*), we found that administration of large-size (200–1000 nm) colloid particles afforded better and easier localization of the SN in breast cancer than small-size tracer particles and that subdermal injection was more suitable than peritumoral administration. This study was performed:

1. To verify our preliminary results in a larger series of patients;
2. To compare subdermal with peritumoral administration of the same tracer; and
3. To compare, in a small subgroup, the lymphatic drainage revealed by subdermal injection of radiolabeled colloids with that revealed by peritumoral injection of blue dye, in the same patients.

MATERIALS AND METHODS

Radiopharmaceuticals

Three kinds of colloid material were used:

1. Antimony sulfide colloid, particle size <50 nm;
2. Colloid particles of human albumin, particle size <80 nm; and
3. Colloid particles of human albumin, particle size range 200–1000 nm.

All colloids were from Amersham-Sorin, Saluggia, Italy.

The particles were reacted with ^{99m}Tc freshly eluted from a generator at a concentration of 1 mCi/ml. The product was checked for free technetium according to the manufacturer's instructions; in all cases, >95% of the technetium was bound to colloid. Each patient received 7 MBq ^{99m}Tc-labeled material.

TABLE 1
Clinical Characteristics of 250 Breast Cancer Patients who Underwent Lymphoscintigraphy to Detect the Sentinel Node

Characteristics	Value
Age (yr)	
Mean	52
Range	25–77
Stage, no. (%)	
T1	177 (71%)
T2	48 (19%)
T3	25 (10%)
No. of palpable axillary nodes (%)	77 (31%)

Patients

Two-hundred fifty patients were studied; all had suspected breast carcinoma (stage T_1–T_3) by physical examination, mammography and fine needle aspiration. Pregnant or nursing mothers and patients who had received prior breast surgery, chemotherapy or radiotherapy were excluded. Patient characteristics are summarized in Table 1. The patients were allocated, on a consecutive basis, to one of three groups, each with two subgroups, defined according to type of colloid administered and injection site:

Group Is. Antimony sulfide by subdermal injection (35 patients);

Group Ip. Antimony sulfide by peritumoral injection (15 patients);

Group IIs. Human albumin, <80 nm subdermally (35 patients);

Group IIp. Human albumin, <80 nm peritumorally (15 patients);

Group IIIs. Human albumin 200-1000 nm subdermally (105 patients); and

Group IIIp. Human albumin 200-1000 nm peritumorally (45 patients).

The tracer was injected the day before surgery and was followed by lymphoscintigraphy to reveal lymphatic drainage from the tumor and to locate the SN.

Administration of Colloid

Peritumoral administration was performed by parenchymal injection around the breast mass using a long 25-gauge needle. Subdermal administration was performed by injection above the breast lesion using a short 25-gauge needle. For nonpalpable tumors, the lesion was localized by mammography or ultrasound. After injection, the patient was instructed to massage the injection site for 2 min.

Injection Volume

For the first 30 patients (10 from each group), tracer was injected in a volume ranging from 0.2 to 3 ml. Subsequently, injection volumes were standardized at 0.4 ml for subdermal and 0.5 ml for peritumoral injection (see the Results section). In all cases, the radiolabeled colloid suspension was diluted with physiologic saline.

Lymphoscintigraphy

Planar scintigraphic scans of the involved breast and axillary region, in anterior and anterior–oblique projections, were obtained 15–30 min and 3 hr after radiotracer injection. Acquisition time was 5 min. After acquisition of the last scan, the skin projection of the first node to take up tracer (defined as the SN) was marked with a suitable pen while the patient was supine with arm extended laterally at 90° to the body. An additional planar scan was taken immediately before surgery if no tracer had been observed in the axillar region the day before. The hot spot(s) on the scintigraphic image were marked off and analyzed by regions of interest to calculate SN uptake as a percentage of the dose at the injection site.

Gamma Ray Detecting Probe

The GDP was a C-Trak System, from Care-Wise (Morgan Hill, CA) or a SCINTI-PROBE MR 100, from Pol.hi.tech. Carsoli (L'Aquila, Italy). Radioactivity detected by the probe was transduced into digital readout and acoustic signals. The intensity and frequency of the acoustic signal were directly proportional to the level of radioactivity.

Lymph Node Biopsy

After the primary tumor had been removed, the GDP was used to precisely locate the skin projection of the node emitting the greatest radioactivity, using the skin mark as a guide. The skin was incised directly over this point, and using the GDP to guide dissection, we excised and tagged the node emitting the highest activity as the SN. Sometimes two or more nodes were picked up by the probe and were removed. Once removed, however, the specimen was rechecked by the probe and only the node with the highest radioactivity labeled as the SN. Complete axillary dissection was then performed.

Lymphatic Mapping with Isosulfan Blue

In 40 patients scheduled to receive quadrantectomy who underwent subdermal lymphoscintigraphy, the dye isosulfan blue was injected into the tumor bed immediately after excision of the primary, using a 25-gauge needle; 3 ml dye were administered in four injections. The lymph tract revealed by the dye was dissected until the blue axillary node was located.

Pathologic Examination

All nodes removed from the axilla (the three classic levels, plus the separately tagged SN) were examined using a standard technique. Briefly, the nodes were freed from fat tissue, and those that were >0.5 cm in diameter were bisected longitudinally, whereas those that were <0.5 cm in greatest diameter were embedded whole. Three different sections were obtained (0.3–1 mm apart) and stained with hematoxylin and eosin.

Statistical Analysis

Numeric data are reported as means ± s.d.

Statistical analysis was performed using ANOVA and the chi-square test when appropriate.

RESULTS

Sentinel Node Lymphoscintigraphy

In 5 of the 250 patients (2%; 2 from Group Is and 3 from Group Ip), no drainage pattern was revealed by lymphoscintigraphy. In these patients, injection volumes were in the range 1–3 ml; the tumors were T_1N_0 (2 tumors), T_2N_0 (1 tumor) and T_2N_1 (2 tumors). In 5 other patients, drainage was to the internal mammary nodes, which were not dissected.

In the remaining 240 patients, drainage was to the ipsilateral axilla and was revealed by lymphoscintigraphy. Within this series, the number of nodes revealed was in the range 1–5 nodes (mean = 2 nodes), with a significant difference between the three tracer-defined groups: Group I, 2.1 ± 1.1; Group II, 1.6 ± 0.8; and Group III, 1.3 ± 0.5 (analysis of variance, p < 0.001). However, there was no difference according to administration of the same tracer (Table 2).

When tracer was administered subdermally, lymphoscintigraphy revealed one or more nodes within 30 min in 81% of patients. When tracer was administered peritumorally, the detection time was longer: in 60%, the detection time was within 30 min, and in 12%, it was 4–18 hr later (p < 0.001). When lymphoscintigraphy revealed more than one node, the

TABLE 2
Number of Lymph Nodes Revealed by Lymphoscintigraphy in 240 Patients

| Group	Subdermal injection (mean ± s.d.)	Peritumoral injection (mean ± s.d.)	Total (mean ± s.d.)
I	2.0 ± 1.1	2.2 ± 1.3	2.1 ± 1.1
II	1.5 ± 0.7	1.7 ± 1.0	1.6 ± 0.8
III	1.3 ± 0.5	1.2 ± 0.4	1.3 ± 0.5
Total	1.5 ± 0.8	1.5 ± 0.9	1.5 ± 0.8

p < 0.001.

first node to become active always showed the highest uptake both in the early and later images (Figs. 1 and 2). Tracer uptake by SN as a percentage of the injected dose was lower after peritumoral injection (mean = 0.1% ± 0.04%) than after subdermal injection (mean = 0.9% ± 0.5%), especially when large injection volumes were used (Fig. 3). The lymphatic channels were more often delineated after subdermal than peritumoral injection (Fig. 4).

### Sentinel Lymph Node Biopsy and Lymph Node Dissection

Gamma ray detecting probe-guided localization and removal of SNs was successful in all 240 patients in whom tracer uptake by axillary lymph nodes was observed by lymphoscintigraphy. In this series, the primary tumor was removed by quadrantectomy (213 patients, 89%) or mastectomy (27 patients, 11%), followed in all cases by complete axillary dissection. Mean values of 25 ± 6.3 lymph nodes and 1.4 ± 0.6 SNs were removed per patient, with a significant difference between Group I (mean = 1.7 ± 0.8) and both Group II (mean = 1.4 ± 0.6) and Group III (mean = 1.4 ± 0.6)

In 108 of 240 patients (45%), the SN was metastatic, and in 41 of 108 (38%), the SN was the only metastatic node. In 67 other cases, both SN and one or more other nodes were metastatic. In 98 patients, axillary Level I was the only site of metastasis; in 9 patients, Levels I and II were involved; and one patient Level III was also involved. There were no skip metastases in the latter 10 patients.

In 132 of 240 (55%) patients, the SN was negative; in 126 of these patients, the axilla was free of disease, whereas in 6, other
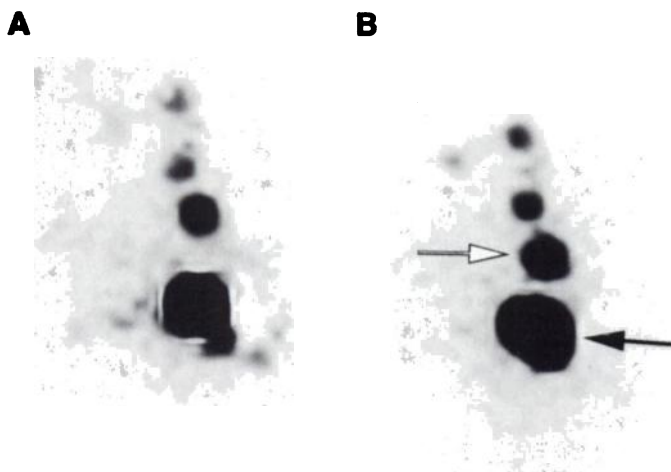
FIGURE 1. Early (A) and later (B) scintigraphic images in anterior view after subdermal injection of ⁹⁹ᵐTc-labeled antimony sulfide colloid to upper outer quadrant of left breast. Several nodes are revealed in the axilla. Injection site (black arrow) and SN (open arrow) are marked.
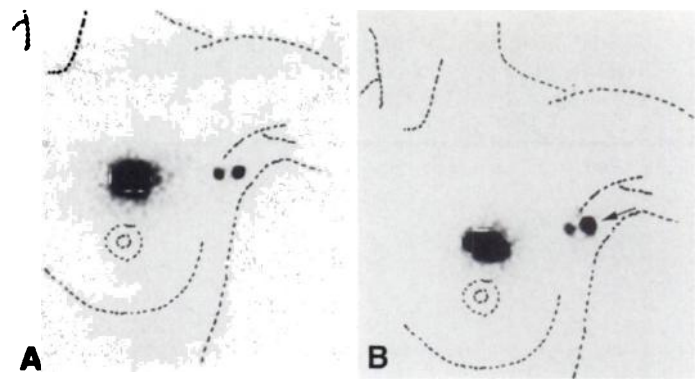
FIGURE 2. Left anterior–oblique scintigraphic scans acquired after peritumoral injection of ⁹⁹ᵐTc-labeled colloid particles (<80 nm) to upper outer quadrant of left breast. (A) Image acquired at 30 min showing two hot spots in the axilla. (B) Image 3 hr postinjection: the SN (arrow) is identifiable as the most radioactive spot.

axillary nodes were involved. Three of these six false-negative cases were associated with multifocal cancers (cribriform, lobular and ductal carcinoma). Subdermal antimony sulfide was given in two of these three cases (Group Is), and peritumoral <80 nm albumin was administered in the other case (Group IIp); in one of these, there was a skip metastasis. In the remaining three cases (two Group IIp and one Group IIIs), invasive ductal carcinoma was found, one of which presented skip metastasis. In 234 of 240 (97.5%) patients, there was a concordance between SN status and axillary lymph node status.

Blue dye injection was successful in locating the SN in 30 of 40 patients (75%). In 26 of 40 (65%), the same nodes were identified by lymphoscintigraphy and blue dye; in 10 patients (25%), the SN was identified only by GDP; and in 4 patients (10%), different nodes were identified by the two techniques. None of the latter 4 patients had axillary disease.

Dosimetry

The absorbed doses to the inoculated area and lymph nodes (both of which were removed surgically) were estimated at 0.70 ± 0.45 mGy/MBq and 0.03 ± 0.02 mGy/MBq, respectively. Because of the small quantity of material injected and the fact that it was mainly concentrated in tissue that was removed, the absorbed dose to the breast and other tissues was negligible.

External irradiation to staff were estimated from ionization chamber (Victoreen 450P) measurements of the exposure rate in air. The air kerma rate at 0, 50 and 100 cm from the injection site immediately before surgery (~20 hr after injection) was 4.5 ± 1.0, 1.5 ± 0.4 and 0.9 ± 0.3 μGy/hr, respectively. The absorbed dose to surgeons' hands was calculated as 10 ± 7
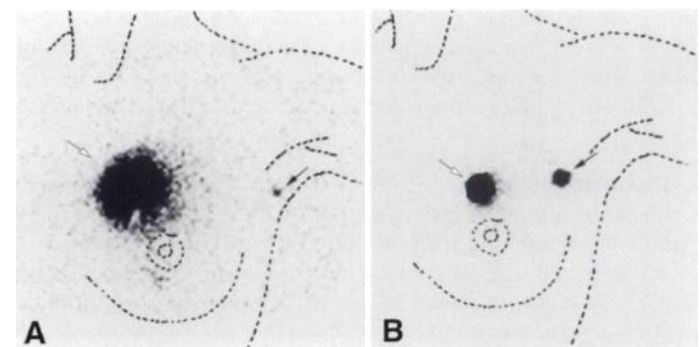
FIGURE 3. Peritumoral injection of ⁹⁹ᵐTc-labeled human albumin colloid, size range 200–1000 nm. Injection volume 1.5 ml in (A) and 0.5 ml in (B). The area of the injected tracer (open arrows) is larger and SN uptake (black arrows) is less intense in A than in B.
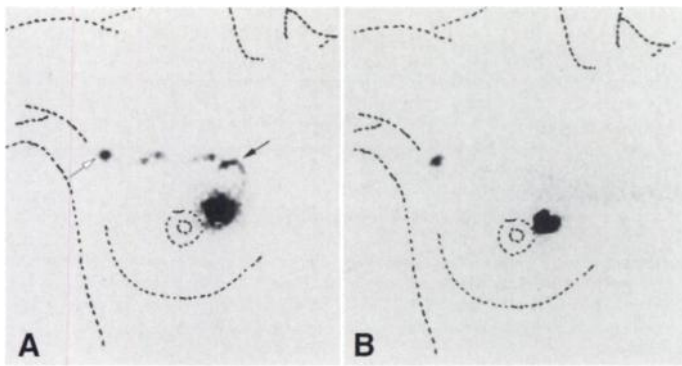
FIGURE 4. Subdermal injection of large-size ^{99m}Tc-labeled albumin colloids to inner lower quadrant of right breast. Early (A) and delayed (B) scintigraphic images in anterior–oblique view. Lymph vessel (black arrow) and SN (open arrow) are seen in A; only SN is evident in later scan.

μSv/hr, which is very low compared to the recommended limits for exposed personnel (17).

The procedure is, therefore, safe and does not involve radiation risk for patients, relatives, surgeons or other hospital personnel.

DISCUSSION

Lymphoscintigraphy is increasingly used to identify the sentinel lymph node in malignant disease, including breast cancer. Use of the original blue dye technique to identify this node has several drawbacks in breast cancer, the most important being that the axilla must be dissected blindly until the blue node, which may be several centimeters from the incision, is seen. The advantage of lymphoscintigraphy is that it allows accurate preoperative localization of the SN, whereas use of a GDP during surgery precisely pinpoints the node and guides dissection, rendering node biopsy easy, rapid and consistently successful.

However, several aspects of the technique remain to be optimized. Although the procedure has been assessed and a methodology has been recommended for melanoma (18), in breast cancer, the optimum tracer, activity, injection volume and administration site have yet to be established. Often the tracer does not move from the injection site. This has been proposed (19,20) to be due to particle agglomeration, perhaps arising from variation in the heating cooling times used in the preparation of the labeled colloid or from the use of technetium eluted from new versus old generators. The proposed solution was to filter commercial colloid preparations. Theoretically, the best colloid for SN localization would be one small enough pass through the lymph vessels promptly, yet large enough to be entirely retained by the SN, which can thereby be easily identified by lymphoscintigraphy and by the GDP during surgery.

In a preliminary study (16), we found that small colloid particles (<50 nm) were often trapped in several nodes and retained in lymphatic vessels, increasing the risk of sampling non-SNs. This finding was confirmed by this study and agrees with the results of other lymphoscintigraphic studies that used small-size antimony sulfide or colloidal albumin (15,21). In contrast, we found that larger particles were often taken up by one node only and tracer retention in that node remained constant up to the time of surgery (16–18 hr later).

Our experience indicates that lymphoscintigraphy should include both anterior and anterior–oblique views: the anterior view is necessary for detection of possible internal mammary chain drainage, which might be useful for other future treatments (radiotherapy), whereas the anterior–oblique view is best

for determining the skin projection of the SN. Scans at 3 hr were important for two reasons:

1. Lymph vessels were often revealed in early scans, obscuring the SN, whereas tracer had usually disappeared from these vessel in later scans; and
2. Tracer movement was often delayed after peritumoral injection and sometimes after subdermal injection.

Local massage may have helped to promote migration. A scan before the operation was necessary if tracer was excessively slow to move, but slow movement generally occurred when large injection volumes were used.

The skin mark defining the position of the SN proved very useful at the beginning of dissection, particularly when more than one node took up tracer. When two lymph nodes were visualized scintigraphically, the SN was always taken as the one that was revealed first, which was always the most radioactive. However, the surgeon often biopsied more than one node, and when this occurred, the specimen was checked after removal, from which it was usually possible to unambiguously identify a single node and label it SN.

Lymphoscintigraphy successfully revealed the lymphatic drainage from the tumor in 245 of 250 (98%) of our patients. In the five unsuccessful cases, a relatively large injection volume (1–3 ml) was used. Large injection volumes (1 ml or more) also tended to be associated to delayed tracer migration from the injection site. We suggest that the low success rate with lymphoscintigraphy reported by El-Shirbiny et al. (22) may have been be due to the use of a large injection volume (4 ml). Increased pressure due to excessive injected fluid may cause collapse and blockage of the local lymph vessels.

After peritumoral administration, we found that intranodal uptake of tracer was often faint and did not always become more prominent in very late images, so that SN identification during surgery was sometimes difficult. On the other hand, with subdermal injection, the SN was always promptly visualized; also, lymph vessels were often seen in the first 5–10 min but usually disappeared from later images. It should be stressed, however, that we found no overall difference between peritumoral and subdermal administration in terms of ability to reveal the SN.

We compared radiocolloid mapping by subdermal injection with blue dye mapping according to the technique of Giuliano et al. (7) in 40 patients. In our hands, the success rate with blue dye was similar to that found by Giuliano et al. (7). In 30 of 40 patients, the SN with the highest radiotracer uptake was the blue node. This may be interpreted as a demonstration that subdermal administration of radiolabeled colloids correctly identifies the SN and implies the existence of connections between superficial and deep lymphatic channels.

In an earlier article introducing our technique of subdermal administration of radiocolloids in 163 patients (23), SN localization was successful in all except three cases (2%), and SNs were falsely negative in 2.5% of those localized. In this study, the SN also correctly predicted the status of the axilla in 97.5% of cases. Both studies suggest that the accuracy of the method can be further improved if patients with multifocal lesions are excluded. Furthermore, extensive metastatic invasion of the axilla is likely to alter lymphatic drainage and impede tracer migration from the injection site, so the technique should only be applied to early cancers, where it is likely to have an accuracy very close to 100%.

CONCLUSION

Lymphoscintigraphy by injecting a small volume (0.4 ml) of radiolabeled colloid (size range 200–1000 nm) can be used in association with GDP-guided SN biopsy to provide reliable information on the state of the axillar for staging purposes. Both the subdermal and peritumoral colloid administration routes are acceptable, although the subdermal route appears superior. The technique is simple to perform, relatively inexpensive and well accepted by patients. We hope that may be used as part of a less-aggressive approach to breast cancer that does not compromise the curative intent of the treatment.

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Fluorine-18-Fluorodeoxyglucose PET Identification of Cardiac Metastasis Arising from Uterine Cervical Carcinoma

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Cardiac metastasis of uterine cervical carcinoma is rare. We describe a patient with a past history of uterine cervical carcinoma who presented with metastasis to the heart, lungs and distant lymph nodes 3 yr after surgery and chemotherapy. Since the patient complained of chest pain and demonstrated electrocardiogram abnormalities, we performed echocardiography, electron beam CT and MRI, which revealed a tumor in the right ventricular wall. The tumor was assessed by 67Ga scintigraphy and 18F-fluorodeoxyglucose (FDG) PET scanning. The mean differential 18F-FDG uptake ratio of the tumor was 7.9, suggesting malignancy, which was later confirmed by myocardial biopsy. Information about the extent of the tumor and partial necrosis within it was provided by 18F-FDG PET.

Although both radionuclide imaging techniques also detected metastatic lesions in the lungs and lymph nodes, 18F-FDG PET scanning detected small lesions more sensitively than 67Ga scintigraphy.

Key Words: heart neoplasm; uterine carcinoma; fluorine-18-fluorodeoxyglucose

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Uterine cervical carcinoma often spreads to the vaginal mucosa and the myometrium of the lower uterine segment (*1*). Sometimes it metastasizes to distant organs such as the lung, bone and brain (*2*), but metastasis to the heart is very rare (*3–6*). In fact, metastatic heart tumors frequently originate from carcinomas of the bronchus and breast, malignant melanoma, lymphoma and leukemia (*7*). Heart involvement usually is detected by pericardial effusion with cardiac tamponade, tachy-